REMARKS

I. Independent claims 1 and 13 have been amended to clarify that the aerogels of the present invention contain the therapeutic agent is dispersed throughout the aerogel particles, not enclosed within sac-like vescisle as taught by the cited prior art.

II. Claims 1 and 5-7 were rejected under 35 USC 103(a) as being unpatentable over Unger (US 6,403,056 B1).

The rejection asserts that:

(i) Unger teaches a method for delivering bioactive agents to a patient and/or treating conditions in a patient comprising administering to a patient a composition comprising a charged lipid, a counter ion, a lipid covalently bonded to a polymer and a bioactive agent (col 2, l. 25-35);

(ii) Unger discloses that "aerogel" refers to generally spherical or spheroidical entities which are characterized by a plurality of small internal voids. The aerogels may be formulated from synthetic materials and/or natural materials, such as carbohydrates or proteins (col. 4, lines 66 to col. 5, line 4);

(iii) Unger also discloses that bioactive agents and therapeutic agents can be used in the preparation for treatment or diagnostic purposes. The said agents are selected from proteins and peptides, such as insulin (col. 6, and col 42, lines 45-67) and non-protein agents such as antibiotics, steroids, antitumor agents, etc (col 43, lines 10-37); and

(iv) Unger discloses physical characteristics of gaseous precursors and diameter of emulsified droplet to form a 10 μm vesicle;

and then argues:

Although Unger reference does not specifically state that aerogel particles are soluble in human pulmanary surfactant, it does disclose that aerogel particles are synthesized from carbohydrates, therefore the solubility

is an inherent property of the carbohydrate particles. Also Unger does not specifically teach the formulations for pulmonary delivery, however "for pulmonary delivery" is an intended use recitation and does not support patentability. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the teachings of Unger by forming the particles for pulmonary delivery because of the benefits of administration of therapeutic agents through inhalationand its ease of use for patients compared to injections, oral and other delivery routes.

This rejection is most strenuously traversed, especially in view of the amendments made to independent Claim 1 herein.

Unger does NOT teach the use of aerogels as drug delivery agents under ANY set of delivery conditions (e.g. pulmonary delivery, intravenous, transdermal, oral, etc.). Unger teaches the formation of VESICLES (sac-like structures) composed of a complex mixture of **charged lipids** and **containing a targeting agent and a therapeutic agent** with the entirety bonded covalently to or stabilized by a polymer (natural or synthetic) to form a drug delivery vehicle which is particularly suited for intravenous injection.

THIS IS NOT APPLICANTS' INVENTION. This combination does not suggest Applicants' invention -- other than by the improper use of hindsight to pick and choose individual words based upon Applicants' teachings.

Unger goes on to refer to a host of other potential modes of delivery, the most relevant of which is the pulmonary inhalation of "gas-filled" vesicles formed by "spray-drying" (also known as ambient pressure drying). Unger does not teach that its VESICLES can possibly be obtained by any other drying technique.

A VESICLE is a singularity – a closed-cell sac-like structure or bladder

that contains or is filled with something. Unger teaches that its therapeutic delivery vehicle is a composition that is contained within and characterized by an enclosing VESICLE structure.

An AEROGEL is simply NOT a VESICLE and one does not suggest the other. On the other hand, an AEROGEL is uniquely characterized as a contiguous, open-celled, mesoporous (typically containing by 2 to 50 x 10^{-9} meter pores on average) solid structure that is filled with a gas (**never a liquid**) at a very high volume percentage (**typically over 90%**). A doped aerogel of the type specified in the present application contains either a molecularly dispersed therapeutic agent or aggregates of therapeutic agent intimately mixed within the solid structure of the particles.

Aerogels have a distinct advantage over dense-walled, closed cell bodies (such as VESICLES) for pulmonary drug delivery because they have a much greater dispersion level of therapeutic agent in the particle volume, and the particles have a much greater aerodynamic diameter due to the very low densities attainable (0.0025 g/cm^3 carbohydrate derived aerogels have been made by Aspen for this purpose).

An aerogel is a material that is prepared by removing solvent from a gel structure **without evaporation** – the structure is uniquely formed by converting the internal gel solvent to a gas via a supercritical (sometimes called "hypercritical") state. The supercritical state is defined as being a state that is above the critical temperature and pressure of a given solvent, and supercritical fluids often have an advantageous combination of solvating power (like a liquid) and diffusivity (similar to a gas). Carbon dioxide is the most common supercritical solvent, although many others can be readily used.

It must be noted that although Unger teaches that its VESICLE walls can

be solid, porous or semi-porous, Unger does not teach that the VESICLE can be an AEROGEL. Rather Unger teaches that the walls of its VESICLE can be composed of aerogel.

An AEROGEL is NEVER formed by spray drying, using a blowing agent, or by remaining filled with fluid as required to make Unger's VESICLES. It would NOT be obvious to anyone, even those highly skilled in the art, that any of the VESICLE preparation methods described by Unger have any relation whatsoever to Applicants' aerogels ***because the invention described by Unger has NO possible aerogel structure as processed***.

A VESICLE is not an AEROGEL.

To one trained in the art, at most Unger teaches that its VESICLE walls can be composed of aerogel precursors, but not that they would form an aerogel structure without being reprocessed (dried) using supercritical conditions.

Unger does NOT teach the presence or use of any carrier which is in any structural form other than that of a VESICLE (closed cell structure containing a singular structural void) and Applicants' aerogels are simply not VESICLES.

Accordingly the rejection of Claims 1 and 5-7 based solely upon Unger must be withdrawn.

III. Claims 2-4 and 8-16 were rejected under 35 USC 103(a) based upon Unger (as discussed above) and Abbott et al (US 6,277,489). The rejection acknowledges that Unger fails to contain any specific teachings on steps of preparation of aerogel particles and Abbott et al is cited in an attempt to overcome that deficiency.

However, the combination simply fails to suggest the presently claimed invention.

Abbot teaches specifically about generating highly ordered, functionalized organic layers (related to SAM's or self-assembled monolayers) on metal particles that enhance chemical recognition phenomena. In particular, these layers are incorporated into silica gel structures to enhance affinity chromatography.

While an aerogel, a high surface area, open-celled mesoporous material can be (but is not necessarily) be composed of a silica gel and "aerogel" is briefly mentioned as a possible host structure (one of many) for these affinity enhancing, layered metal particles, <u>there is no mention in Abbott of drug ANYTHING, let alone DRUG DELIVERY, or anything related to developing a maertial for use within the human body. Clearly then, there is nothing in Abbott et al suggesting that aerogels might effect pulmonary delivery</u>.

Thus the rejection can not remain -- the only basis for combining the two referencves is Applicants' own disclosure - which is impermissable hindsight. The rejection shoudl be withdrawn on this basis alone.

It is absolutely NOT obvious to anyone, even those highly skilled in the art, how a coated metal particle doped structure primarily intended for enhanced chemical RECOGNITION, even in aerogel form, would teach anything about pulmonary drug delivery of a bioresorbable excipient/thera-peutic agent in aerogel form.

Nevertheless, the rejection asserts "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the teachings of Unger on the preparation containing active agent and an aerogel particle by adding the method of producing the aerogel particles and

other active agents suitable for combination with the aerogel particles, as taught by Abbott because of the disclosed benefits of aerogels delivering a bioactive to the patients and the method of producing the aerogel particles and their properties are important in the production of the formulation."

This is incorrect. Unger teaches how to make VESICLES for drug delivery not AEROGELS for drug delivery and Abbott et al fails to teach anything drug delivery by any means. Therefore it does not overcome the deficiencies of Unger as noted above.

Accordingly, further comment is not believed warranted. The rejection should be withdrawn.

Conclusion

Accordingly, an early notice of allowance is solicited for each of Claims 1-16.

Respectfully submitted,

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Claims remaining after amendment

1. (amended) A dispersible dry powder for pulmonary delivery comprising a therapeutically effective amount of a therapeutic agent dispersed throughout aerogel particles which are soluble in human pulmonary surfactant.

2. The powder of Claim 1, wherein the aerogel particle is prepared by supercritical drying at a temperature of less than 40°C.

3. The powder of Claim 1, wherein the aerogel particle contains pores of about 1 to 100 nm.

4. The powder of Claim 1, wherein the aerogel particle has a surface area of about 100 to 1,200 m^2/g.

5. The powder of Claim 1, wherein the aerogel particle has a density of about 0.01 to 0.001 g/cc.

6. The powder of Claim 1, wherein the aerogel particle has a particle size of about submicron up to about 3 microns.

7. The powder of Claim 1, wherein the aerogel particle is a carrier selected from the group consisting of sugars and carbohydrates.

8. The powder of Claim 1, prepared by co-gelling the therapeutic agent with a gel-forming material selected from the group consisting of sugars and carbohydrates.

9. The powder of Claim 1, prepared by the steps of (i) preparing porous gels of a carrier material which is soluble in pulmonary surfactant; (ii)

soaking the porous gels in a solution of the therapeutic agent; (iii) removing the solvent and forming aerogels by supercritical drying; and (iv) comminuting the aerogels.

10. The powder of Claim 1, wherein the therapeutic agent is insulin.

11. The powder of Claim 1, wherein the therapeutic agent is methadone.

12. The powder of Claim 1, wherein the therapeutic agent is naltrexone.

13. A method of treating a disease state responsive to treatment by a thera-peutic agent comprising pulmonarily administering to a subject in need thereof a physiologically effective amount of a dispersible dry powder comprising a therapeutically effective amount of a therapeutic agent dispersed throughout aerogel particles which are soluble in human pulmonary surfactant.

14. The method of Claim 13, wherein the powder is prepared by supercritical drying at a temperature of less than 40°C.

15. The method of Claim 14, wherein the powder is prepared by co-gelling the therapeutic agent with a gel-forming material selected from the group consisting of sugars and carbohydrates.

16. A method of preparing a therapeutic dry powder suitable for pulmonary delivery which comprises supercritical drying at a temperature of less than 40°C. a wet gel containing pores and a therapeutic agent within the pores.